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Chapter 53: Multiple Sclerosis

INTRODUCTION

- *Multiple sclerosis* (MS) is an autoimmune disease causing demyelination of the central nervous system (CNS) and axonal damage. It is categorized based on progression, clinical features, and treatment response.

CLINICAL PRESENTATION

- MS symptoms vary widely between patients and over time.
- Clinical courses include relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS).
- RRMS features relapses with new symptoms lasting ≥24 hours; most RRMS cases eventually progress to SPMS. PPMS is progressive from the onset of the diagnosis.
- MS signs and symptoms are classified as primary, secondary, or tertiary.

PRIMARY SYMPTOMS

- Direct consequence of demyelination.
- These include visual complaints/optic neuritis, gait problems and falls, paresthesias, pain, spasticity, weakness, ataxia, speech difficulties, psychological changes, cognitive changes, fatigue, bowel/bladder dysfunction, sexual dysfunction, and tremors.

SECONDARY SYMPTOMS

- Complications resulting from primary symptoms.
- May include recurrent urinary tract infections, urinary calculi, decubiti and osteomyelitis, osteoporosis, respiratory infections, poor nutrition, and depression.

TERTIARY SYMPTOMS

- These reflect the effect of the disease on the patient's everyday life.
- These include financial, personal/social, vocational, and emotional problems.

DIAGNOSIS

- MS is a diagnosis of exclusion since many conditions can mimic its symptoms.
- Diagnosis requires "lesions separated in space and time," meaning at least two episodes at different CNS sites, unexplained by other causes.
- Magnetic resonance imaging (MRI) is essential; additional tests may support diagnosis **(Fig. 53-1)**.

FIGURE 53-1

Algorithm for management of clinically definite MS. (CIS, clinically isolated syndrome; DMT, disease-modifying therapy; JCV, John Cunningham

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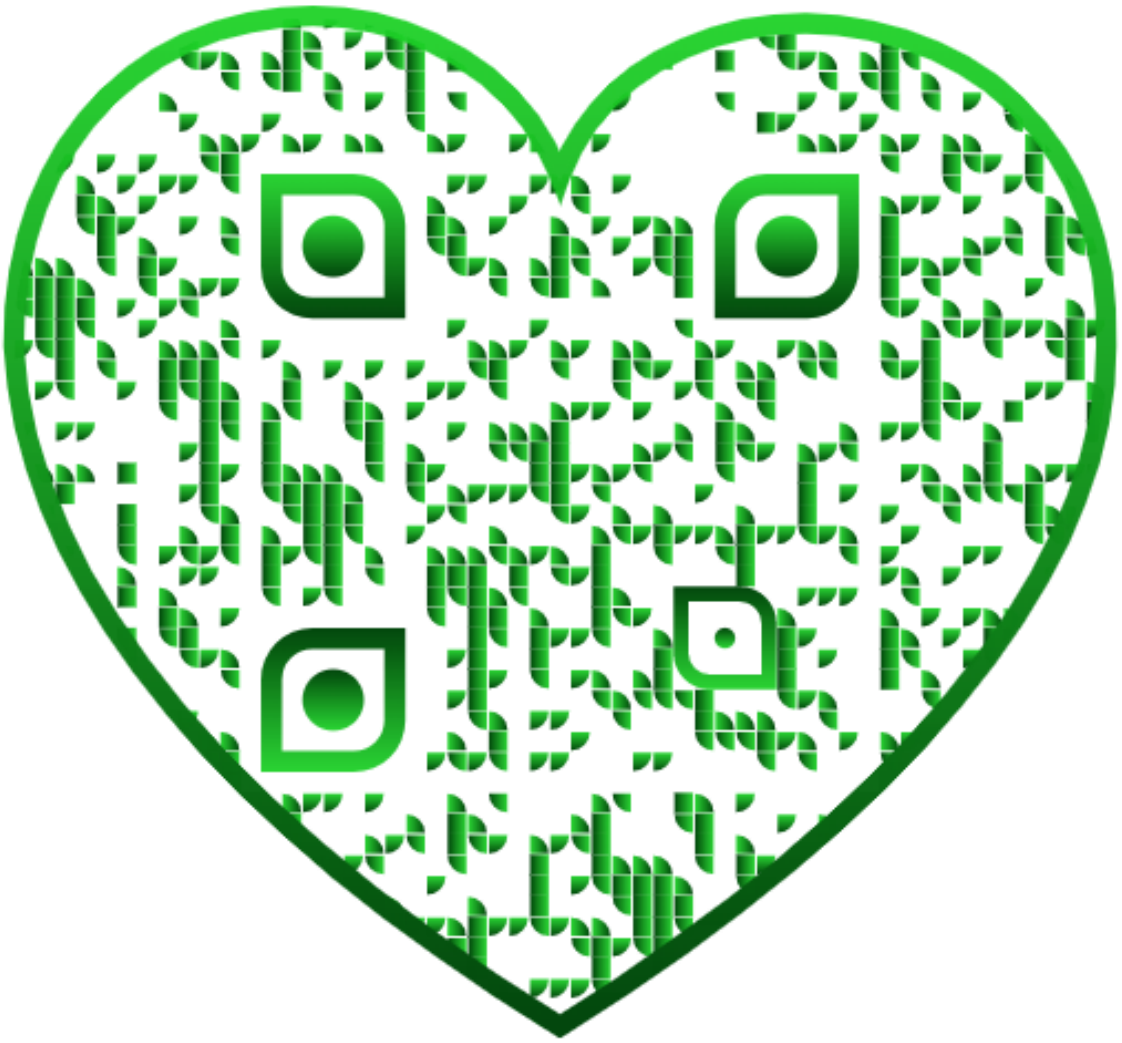

virus; LP, lumbar puncture; PML, progressive multifocal leukoencephalopathy; RIS, radiologically isolated syndrome; Rx, prescription medication.)

TREATMENT

- Goals of Treatment: Improve quality of life, maintain employment, and reduce long-term disability in MS patients.

NONPHARMACOLOGIC THERAPY

- Occupational therapy helps patients adapt to daily activities and stay active.
- Physical therapy improves strength, gait, and balance and reduces spasms; mobility aids like canes or walkers may also be helpful.
- Functional electrical stimulation devices (eg, Bioness, WalkAide, Neural sleeve) can improve nerve or muscle function.
- Psychotherapy and counseling support those with depression, anxiety, or PTSD.

PHARMACOLOGIC THERAPY

- Early RRMS is marked by exacerbations.
- MS treatment includes relapse management, disease-modifying therapies (DMTs), and symptomatic(**Fig. 53-1**).
- Frequent/severe relapses may not need treatment.
- High-dose corticosteroids (**methylprednisolone** 1000 mg IV or orally or **prednisone** 1250 mg orally) are used when function is affected.
- Rule out pseudoexacerbation before treating relapses or changing DMTs.
- DMTs slow disease progression, but symptom management maintains quality of life.
- Guidelines exist, but treatment is tailored to patient preferences.
- **Tables 53-1** and **53-2** detail DMT dosing and monitoring.

TABLE 53-1

Disease-Modifying Therapy

Medication (Brand Name)	Indication	Initial Dose	Usual Dose	Comment
First-Generation Agents				
Self-injectables				
Interferon-β_{1a} (Avonex)	Relapsing forms of MS	30 mcg (6 million IU) IM once weekly	30 mcg IM once weekly	Considered low-potency interferon
(Rebif)	Relapsing forms of MS	22 mcg SQ three times a week	22 or 44 mcg SQ three times a week	Considered a high-potency interferon
Interferon-β_{1b}	Relapsing	250 mcg (8 million IU) SQ every	250 mcg SQ every other day	Betaseron/Extavia: high-potency interferon;

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(Betaseron, Extavia)	forms of MS	other day		limited human data, animal data suggests moderate pregnancy risk.
Pegylated interferon-β_{1a} (Plegridy)	RRMS	6.3 mcg SQ on day 1, then 94 mcg SQ on day 15, then 125 mcg SQ on day 29, then 125 mcg SQ every 14 days	125 mg SQ every 14 days	Premedicate or use antipyretic/analgesic for flu-like symptoms. Animal data show moderate pregnancy risk.
Glatiramer acetate (Copaxone, Glatopa, Clift)	CIS, RRMS	20 mg SQ once daily or 40 mg SQ three times a week	20 mg SQ once daily or 40 mg SQ three times a week	Glatopa and Clift are Copaxone biosimilars; low pregnancy risk, benefits outweigh risk.
IV Infusion				
Mitoxantrone (Novantrone)	SPMS and worsening RRMS	12 mg/m^2 IV every 3 months	12 mg/m^2 IV every 3 months	Lifetime dose should not exceed 140 mg/m^2; contraindicated during the first trimester of pregnancy
Second-Generation Agents				
Oral				
Fingolimod (Gilenya)	Relapsing forms of MS, in patients 10 years and older	Adult: 0.5 mg orally once daily; Pediatric: <40 kg 0.25 mg orally once daily, >40 kg 0.5 mg orally once daily	Adult: 0.5 mg orally once daily; Pediatric: <40 kg 0.25 mg orally once daily, >40 kg 0.5 mg orally once daily	Medication guide required; limited human data for pregnancy risk
Siponimod (Mayzent)	Relapsing forms of MS	CYP2C9 *1/*1, *1/*2, *2/*2: 0.25 mg once daily on days 1 and 2, then 0.5 mg once daily on day 3, then 0.75 mg once daily on day 4, then 1.25 mg once daily on day 5 CYP2C9 *1/*3, *2/*3: 0.25 mg once daily on days 1 and 2, then 0.5 mg once daily on day 3, then 0.75 mg once daily on day 4	CYP2C9 *1/*1, *1/*2, *2/*2: 2 mg once daily beginning on day 6 CYP2C9 *1/*3, *2/*3: 1 mg once daily beginning on day 5	Medication guide required; may cause fetal harm; CYP2C9 genotype testing required prior to initiating dose
Ozanimod (Zeposia)	Relapsing forms of MS	0.23 mg once daily on days 1–4, then 0.46 mg once daily on days 5–7	0.92 mg once daily beginning on day 8	Medication guide required; may cause fetal harm
Ponesimod (Ponvory)	Relapsing forms of MS	2 mg on days 1 and 2, 3 mg on days 3 and 4, 4 mg on days 5 and 6, 5 mg on day 7, 6 mg on day 8, 7 mg on day 9, 8 mg on day 10, 9 mg on day 11, 10 mg on days 12–14	20 mg on day 15 and thereafter	Medication guide required; may cause fetal harm

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Dimethyl fumarate (Tecfidera)	Relapsing forms of MS	120 mg delayed release twice daily for 7 days	240 mg delayed release twice daily	Limited human data for pregnancy risk
Diroximel fumarate (Vumerity)	Relapsing forms of MS	231 mg twice daily for 7 days	462 mg twice daily	May cause fetal harm based on animal data
Monomethyl fumarate (Bafiertam)	Relapsing forms of MS	95 mg twice daily for 7 days	190 mg twice daily	May cause fetal harm based on animal data
Teriflunomide (Aubagio)	Relapsing forms of MS	7 mg orally once daily	7 or 14 mg orally once daily	Cholestyramine and charcoal speed elimination. Contraindicated in pregnancy.
Cladribine (Mavenclad)	RRMS and active SPMS	Total 3.5 mg/kg over 2 years: 1.75 mg/kg per year, divided into two 4–5-day cycles (max 20 mg/day). First-year: start first cycle anytime, second cycle 23–27 days after first.	Second-year: Start first cycle ≥43 weeks after last first-year dose; second cycle 23–27 days after first. No oral cladribine for 2 years after completing 2 years of treatment.	Medication guide required. Contraindicated in those of reproductive potential. Lymphocytes must be normal before first course and >800 cells/mm^3 before second course.
IV Infusion				
Natalizumab (Tysabri)	Relapsing forms of MS	300 mg IV every 4 weeks	300 mg IV every 4 weeks	REMS program required; limited human data for pregnancy risk
Alemtuzumab (Lemtrada)	RRMS	First treatment course: 12 mg/day IV for 5 consecutive days (60 mg total dose)	Second treatment course: 12 mg/day IV for 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course	REMS required. Limited pregnancy data. May premedicate with 1000 mg methylprednisolone (or equivalent) before infusion for first 3 days. Start herpes prophylaxis on day one, continue for ≥2 months or until CD4+ ≥200 cells/mm^3, whichever is longer.
Ocrelizumab (Ocrevus)	Relapsing forms of MS and PPMS	First course: 300 mg IV, then 300 mg IV after 2 weeks. Begin at 30 mL/hr, increase by 30 mL/hr every 30 min as tolerated, max 180 mL/hr over ≥2.5 hours.	Maintenance: 600 mg IV every 6 months, start at 40 mL/hr, increase by 40 mL/hr every 30 min to max 200 mL/hr over at least 3.5 hours.	Fetal risk possible. Premedicate with antihistamine (30–60 min before) and 100 mg methylprednisolone (or equivalent, 30 min before). Optional antipyretic. Observe 1 hour postinfusion.
Ublituximab (Briumvi)	Relapsing forms of MS	First treatment course: 150 mg once on day 1, followed by 450 mg once 2 weeks later	Subsequent treatments: 450 mg every 24 weeks, starting 24 weeks after initial 150 mg dose.	May cause fetal harm. Premedicate: antihistamine 30–60 min before, 100 mg methylprednisolone (or equivalent) 30 min before infusion; consider antipyretic. Observe for 1 hour after first two infusions.
Self-injectable				
Ofatumumab (Kesimpta)	Relapsing forms of MS	20 mg once weekly for 3 doses (weeks 0, 1, and 2)	20 mg once monthly starting at week 4	Medication guide required; single-dose prefilled syringe pen; based on animal data, it may cause

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				fetal harm
Ocrelizumab and Hyaluronidase (Ocrevus Zunovo)	Relapsing forms of MS and PPMS	920 mg/23,000 units SQ once	920 mg/23,000 units SQ once every 6 months	Fetal risk possible. Premedicate 30 min before infusion with antihistamine and 20 mg dexamethasone (or equivalent); consider an antipyretic. Observe 1 hour after initial dose, 15 min after later doses.

CIS, clinically isolated syndrome; IM, intramuscular; REMS, Risk Evaluation and Mitigation Strategy; SQ, subcutaneous; IU, international units.

TABLE 53-2

Adverse Effects and Monitoring Parameters

Medication	Adverse Effects	Monitoring Parameter	Comments
Interferon-β_{1a}	Depression, flu-like symptoms, leukopenia, injection site reactions	Electrolytes, CBC, LFTs, thyroid, LVEF, depression, and LFTs at baseline, 1 month, every 3 months for 1 year, then every 6 months	Avoid use in untreated severe depression
Interferon-β_{1b}	Depression, injection site reactions, leukopenia, flu-like symptoms	Electrolytes, CBC, LFTs, thyroid function, depression	Avoid use in untreated severe depression; more frequent injection site reactions reported
Glatiramer acetate	Injection site reactions, infection, hypersensitivity, chest tightness, urticaria	MRI, tissue necrosis, postinjection reaction	Chest tightness, urticaria can occur at any dose
Mitoxantrone	Bone marrow suppression, neutropenia, cardiotoxicity, AML, nausea, vomiting, diarrhea, alopecia	CBC, ECG, LVEF, LFTs	Secondary leukemia; lifetime maximum dose due to cardiac toxicity
Fingolimod	Lymphocytopenia, macular retinal edema, AV block, infection, headache	CBC, ECG, varicella zoster antibody, blood pressure, ophthalmic examination, LFTs	First dose requires 6-hour observation. Contraindicated with Class I/III antiarrhythmics, recent cardiac diseases,[a] or AV block. Ketoconazole increases levels. Vaccines may be less effective. Monitor for rebound after stopping
Siponimod	Infections, macular edema, bradyarrhythmia and atrioventricular conduction delays, decreased pulmonary function, liver injury, increased blood pressure	CBC, ECG, varicella zoster antibody, blood pressure, ophthalmic examination, LFTs	Requires CYP2C9 genomic testing. Contraindicated in *3/*3 genotype; medication interactions with 2C9 and 3A4 inhibitors and inducers
Ozanimod	Infections (URTI), AV block, bradycardia, hepatotoxicity, increased blood pressure, lymphopenia, macular edema, neurotoxicity, PML, decreased pulmonary function, varicella zoster infections	CBC, ECG, varicella zoster antibody, blood pressure, ophthalmic examination, LFTs	Avoid with strong CYP2C8/BCRP inhibitors or inducers. No live attenuated vaccines during and for 3 months after treatment

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Ponesimod	Infections, bradyarrhythmia and atrioventricular conduction delays, pulmonary function, liver injury, increased blood pressure, cutaneous malignancies, macular edema	CBC, ECG, LFTs, ophthalmic examination, varicella zoster antibody	Contraindicated with recent cardiac diseases,[a] second- and third-degree AV block, sick sinus syndrome, or sinoatrial block (unless pacemaker present); monitor high-risk patients for 4 hours
Dimethyl fumarate	Flushing, rash, pruritus, GI discomfort, lymphocytopenia, increased LFTs, albuminuria, PML	CBC, LFTs, MRI	Taking with food decreases the incidence of flushing
Diroximel fumarate	Flushing, GI upset, hepatotoxicity, infections, lymphopenia, PML	CBC, LFTs, MRI	Fewer GI adverse effects than dimethyl fumarate; may be better tolerated
Monomethyl fumarate	Flushing, GI upset, hepatotoxicity, infections, lymphopenia, PML	CBC, LFTs, MRI	Fewer GI adverse effects than dimethyl fumarate; may be better tolerated
Teriflunomide	Steven-Johnson syndrome, liver failure, neutropenia, respiratory infection, activation of TB, alopecia, neuropathy	CBD, LFTs, blood pressure, pregnancy, TB test	Contraindicated in severe liver impairment. May reactivate TB. Active metabolite of leflunomide. Rapid elimination (charcoal/cholestyramine) needed if pregnant
Cladribine	Bone marrow suppression, cardiotoxicity, hepatotoxicity, infection, malignancy, neurotoxicity, PML, renal toxicity, hypersensitivity, headache	CBC: baseline, 2 and 6 months after each cycle, then periodically. Screen for HIV, HBV, HCV, TB, VZV, pregnancy; check LFTs, MRI; monitor for PML, infection	Contraindicated with current malignancy, HIV infection or active chronic infections, pregnancy, and lactation
Natalizumab	PML, depression, fatigue, respiratory infection, arthralgia, hepatotoxicity	JCV antibody, infection, MRI, LFTs, hypersensitivity reactions	Risk of PML; risk of IRIS when discontinued due to PML; monitor for rebound disease activity with sudden cessation
Alemtuzumab	Infusion reactions, infections (nasopharyngitis, UTI, URI, herpes viral infections), autoimmune disorders, thyroid disorders, immune-mediated thrombocytopenic purpura, Goodpasture syndrome	CBC, thyroid function, antibodies to varicella zoster virus, HPV screening, serum creatinine, TB prior to treatment, infusion reactions, skin exams, urinalysis	Contraindicated in HIV. Use birth control during and 4 months after treatment. Avoid nursing during and for 4 months after treatment
Ocrelizumab	Infusion reactions, nasopharyngitis, upper respiratory tract infection, headache, UTI, herpes virus–related infections, neoplasms	MRI, active infection before infusion, infusion reactions during and after infusion, skin infections	Live vaccines not recommended during or after treatment until B-cell recovery; give live vaccines 6 weeks before treatment. Screen for hepatitis B before first dose
Ublituximab	Infusion reactions, nasopharyngitis, upper respiratory tract infection, headache, UTI, herpes virus–related infections, neoplasms	MRI, active infection before infusion, infusion reactions during and after infusion	Give live vaccines 6 weeks before treatment; not advised during or after treatment until B-cell recovery. Screen for hepatitis B before first dose. Avoid pregnancy during and for 6 months after treatment. Contraindicated in active HBV or previous life-threatening infusion reaction to Briumvi
Ofatumumab	Infections, injection site reactions, reduction in immunoglobulins,	HBV screen, serum immunoglobulins, CBC, PML,	Contraindicated in active HBV. Immunize ≥4 weeks before starting for live/attenuated vaccines, ≥2 weeks for

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	headache	MRI	inactivated

AML, acute myeloid leukemia; CBC, complete blood count; ECG, electrocardiogram; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; LFT, liver function test; LVEF, left ventricular ejection fraction; PML, progressive multifocal leukoencephalopathy.

[a]Cardiac disease, including myocardial infarction, unstable angina, stroke, transient ischemic attack, and heart failure NYHA Class III/IV.

Disease-Modifying Therapy (DMT)

- DMTs are either immunomodulatory (alter immune signals without cytotoxicity) or immunosuppressive (directly cytotoxic or cause bone marrow suppression).
- First-generation DMTs include four **interferons** and **glatiramer acetate.**
- Multiple Food and Drug Administration (FDA)-approved treatments for relapsing MS include **mitoxantrone, natalizumab, fingolimod, siponimod, ozanimod, ponesimod, teriflunomide, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, cladribine, alemtuzumab, ocrelizumab, ublituximab,** and **ofatumumab.**
- Ocrelizumab is approved for PPMS; mitoxantrone for progressive or worsening MS.
- These are high-cost specialty drugs, only available through specialty pharmacies.
- DMT effectiveness varies from patient to patient and over time.
- Some DMTs carry progressive multifocal leukoencephalopathy (PML) risk and require Risk Evaluation and Mitigation Strategy (REMS) enrollment.
- Evidence-based DMT recommendations and key questions on initiation, switching, and cessation are in **Table 53-3**.
- DMTs slow progression but do not fully suppress disease; early treatment is most effective.
- Most untreated patients develop progressive, irreversible axonal damage over time.

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TABLE 53-3

Key Recommendations on Treatment and Access Considerations

- Start FDA-approved DMT promptly after relapsing MS diagnosis; consider for some with progressive MS.
- Initial or alternative DMT choice should involve shared decision-making between clinician and patient.
- Clinicians should assess adherence barriers and educate patients on its importance.
- Continue therapy unless no benefit, intolerable adverse effects, increased risk, poor adherence, better options, or decreased inflammatory risk (eg, immunosenescence).
- No relapses on treatment is not a reason to stop therapy. If switching DMTs for suboptimal response, select one with a different mechanism.
- For highly active MS, prescribe high-efficacy therapies like ofatumumab, ocrelizumab, ublituximab, or natalizumab.
- Start natalizumab in MS patients with positive anti-JCV antibodies only if benefits outweigh PML risk.
- Ocrelizumab may be used for PPMS if benefits outweigh risks.
- Discuss family planning at every visit with reproductive-age patients. Usually, stop DMTs before conception. For rebound-risk meds (eg, S1P modulators, natalizumab), consider bridging before conception. If exposed during pregnancy, stop most DMTs unless MS risk outweighs DMT risk.
- Given variability in MS response, contraindications, risk tolerance, and adherence, patient and clinician access to all therapies is essential, affecting administration route and adverse effect tolerance decisions.
- Medication access should not be restricted by relapse frequency, age, personal factors, or disability. Do not delay therapy for insurance approval, as this increases disease risk.

Symptomatic Management

- Primary symptom management of MS is detailed in **Table 53-4**.

TABLE 53-4

Treatment of Select Primary MS Symptoms

Spasticity	Baclofen, Dantrolene, Diazepam, Clonazepam, Tizanidine, Tiagabine, Gabapentin, Pregabalin, Botulinum toxin type A, Dalfampridine
Bladder symptoms	Propantheline, Oxybutynin, Dicyclomine, DDAVP, Imipramine, Amitriptyline, Prazosin, Terazosin, Botulinum toxin type A, Solifenacin, Darifenacin, Trospium, Hyoscyamine, Mirabegron, Tamsulosin, Tolterodine, Self-catheterization
Sensory symptoms	Carbamazepine, Phenytoin, Amitriptyline; other TCAs, Gabapentin, Lamotrigine, Pregabalin, Duloxetine
Fatigue	Amantadine, Antidepressants, Modafinil, Methylphenidate, Dextroamphetamine, Armodafinil, Fluoxetine

DDAVP, desmopressin acetate; TCA, tricyclic antidepressant.

Complementary and Alternative Therapies for MS

- Oral cannabis extract has a level A recommendation (established efficacy).
- Synthetic THC, Sativex spray, and magnetic therapy are level B (probably effective).
- Other complementary and alternative therapies have been used but are not effective or have insufficient evidence.

Vaccine Recommendations

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- Avoid live vaccines in patients on DMTs; safe vaccines include HPV, tetanus, rabies, COVID-19, and inactivated polio.
- An annual flu shot is recommended; avoid live intranasal flu vaccine.
- Use Shingrix (not live) for varicella instead of Zostavax.
- Vaccinate high-risk, unvaccinated patients for hepatitis B before starting ocrelizumab.

EVALUATION OF THERAPEUTIC OUTCOMES

- Acute MS exacerbation treatment often shows response within days.
- Outcomes are tracked over months to years via relapses, hospitalizations, disease progression, and disability scales like Expanded Disability Status Scale (EDSS).
- Set realistic goals and expectations, discuss possible adverse reactions, and involve patients in monitoring outcomes to boost adherence.
- Each DMT requires specific safety and lab monitoring, regular neurologic exams, and checks for side effects or disability changes.
- Some DMTs require REMS or medication guides for safety monitoring.

See Chapter 78, Multiple Sclerosis, authored by Jacquelyn L Bainbridge, Enrique Alverez, Anna A. Shah, Sarah N. Rajkovic, Owen S. Miller, Nicole L. Semmler and Ethana A. Lam, for a more detailed discussion of this topic.

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